

Dapivirine Vaginal Ring for HIV Prevention in Women in South Africa

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Young women remain disproportionately affected by the HIV epidemic in South Africa. Clinical trials have shown that the dapivirine vaginal ring (DVR) is safe and effective at reducing HIV infection in women. In March 2022, the South African Health Products Regulatory Authority approved the use of the DVR in women aged 18 years and older who are unable or unwilling to use oral pre-exposure prophylaxis, as an additional choice for preventing HIV in women at substantial risk. Modelling studies have suggested that the DVR could have a substantial impact if prioritized for women at substantial risk of HIV or women aged 22–29 years. The licensing of the DVR in South Africa is a milestone event that brings the first long-acting and woman-controlled HIV prevention method another step closer to reaching the people who need it. As South Africa prepares its introduction, it is critical to examine the unmet need for HIV prevention and to review the clinical trial data that led to the DVR's approval.

Keywords

AGYW, choice, clinical trials, long acting PrEP, microbicide, review

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While the global commitment to treating HIV has saved countless lives, efforts to prevent new HIV infections have not been so fruitful. The annual number of new HIV infections among adults worldwide has barely changed over the past 5 years, with a disappointing 31% decline since 2010, much lower than the 75% target for 2020 that was mandated by the United Nations General Assembly in 2016.¹ Failing to meet these targets speaks to the need to focus on preventing HIV, as well as on innovation and choice.² In sub-Saharan Africa, gender inequality, discrimination and subsequent disempowerment deny women and girls autonomy and safety. Consequently, young women (aged 15–24 years), who represent 10% of the population, accounted for 25% of HIV infections in 2020.³ Sexual violence is reported by more than a third of women in the region, and these women are more likely to acquire HIV than women who have not experienced violence.⁴ This reality – that few women have the power to negotiate sexual activity or condom use with partners – highlights the need for women to have agency for self-protection.

South Africa has the largest HIV epidemic in the world. In 2018, almost 8 million people in South Africa were living with HIV.⁵ Results from the recent Evidence for Contraceptive Options and HIV Outcomes trial conducted in Eswatini and South Africa highlight the high rates of HIV among women attending family-planning clinics, and show that more effort is needed to integrate HIV prevention strategies for women receiving sexual and reproductive health services.⁶ In the KwaZulu-Natal province, the annual incidence of HIV is as high as 8% in young women aged 20–24 years.⁷ Despite the implementation of highly efficacious HIV prevention tools, the incidence rate remains stubbornly high. These interventions include oral pre-exposure prophylaxis (PrEP), which can reduce HIV acquisition by 90%, medical male circumcision, and the scale-up of HIV treatment, limiting onward transmission to sexual partners.^{8,9} While huge progress has been made in South Africa with initiating anti-retroviral therapy, the level of coverage in the population required to eliminate transmission has not been attained, and women need self-controlled prevention methods that do not rely on daily pill taking. Long-acting products that reduce the burden of adherence are particularly needed.¹⁰

Microbicides are products that can be applied topically in the vagina or rectum to reduce HIV transmission.¹¹ These products have great potential to empower women to protect themselves, as they are easy to use and do not require the consent or cooperation of a partner for use. Even though more than 60 candidate products have been trialled,¹¹ only the dapivirine vaginal ring (DVR) has been successfully licensed worldwide. Two pivotal phase III clinical trials^{12,13} have shown that the DVR is safe and effective at reducing HIV infection in women, and in March 2022, the South African Health Products Regulatory Authority (SAHPRA) authorized the use of the DVR in women aged 18 years and older who are unable or unwilling to use oral PrEP.¹⁴ As South Africa prepares for the introduction of the first woman-controlled, long-acting HIV prevention method, it is critical to examine the unmet need for HIV prevention, review the clinical trial data that led to the DVR's approval, and understand the potential impact of the DVR.

About the dapivirine vaginal ring

The monthly DVR is the first discreet, long-acting HIV prevention product designed specifically for women. It was developed by the International Partnership for Microbicides (IPM) through an exclusive licence for dapivirine from Janssen Sciences Ireland UC.¹⁵ Work on the DVR began in 2004, with feasibility studies followed by research to determine dosing levels and to identify delivery platforms that would support correct and consistent use.¹⁶ Dapivirine gel and other formulations were developed and tested in preclinical and clinical trials. Several ring prototypes were also tested, resulting in the current ring design: dapivirine ring-004.¹⁶

This DVR has a flexible silicone matrix design that provides sustained release of dapivirine, a non-nucleoside reverse transcriptase inhibitor, over 28 days.¹⁷ It contains 25 mg of dapivirine distributed throughout the silicone matrix.¹⁶ The pharmacokinetics of dapivirine delivered by this ring were assessed in healthy participants; dapivirine was detectable in vaginal fluids by 1.5 hours post-ring insertion. Despite the substantial inter-individual variation, the mean maximum concentrations were reached by Day 1 in vaginal fluids and 7 days in plasma.¹⁸ Early-phase trials demonstrated that only a small amount of dapivirine is released over 28 days (approximately 4 mg) and, therefore, the DVR has a favourable pharmacokinetic profile for use as a monthly microbicide.¹⁹

The DVR has only been studied for preventing HIV, in those assigned female at birth, during receptive vaginal intercourse; it does not prevent HIV acquisition through any other mode of transmission.²⁰ However, the DVR is safe and reduces HIV risk.^{12,13} The DVR can be self-inserted and used discreetly, and should be worn continuously for 28 days when placed high in the vagina. It provides no residual protection once removed.

The DVR works at the site of possible infection and has low systemic absorption,² decreasing the likelihood of side effects and drug interactions.^{21,22} The most commonly reported side effects in DVR studies include vaginal itching, urinary tract infection, vaginal discharge and lower abdominal pain.^{12,13,23} Most side effects reported in clinical trials were mild to moderate. The DVR does not protect against sexually transmitted infections (STIs) and pregnancy, and like other oral forms of pre-exposure HIV prevention, should be offered as part of a combination prevention package that includes HIV counselling and testing, condoms and lubricants, STI screening and contraception.

Pivotal phase III efficacy studies

Two pivotal phase III studies (Ring and ASPIRE) conducted in eastern and southern Africa found that the DVR administered monthly reduced the risk of HIV-1 infection in women and was well tolerated with long-term use.^{12,13} The Ring study found an overall 35% reduced risk of HIV,¹² and ASPIRE found that the DVR reduced risk by 27%.¹³ In both trials, the reduction in acquiring HIV was greater among participants who used the DVR more consistently. No reduction in acquiring HIV was seen in women under 21 years, likely due to low adherence in this cohort.^{12,13}

While neither phase III study demonstrated any significant between-group differences in primary safety outcomes, incident STIs or adverse events, the ASPIRE study reported 94 instances of social harm in 4,680 person-years of follow-up (<5% of women), of which 93% were partner related.²⁴ Younger women (age 18–26 years) were twice as likely to report social harm than older participants, and reporting a social harm by a male partner was associated with a short-term lower adherence to the DVR.²⁴

Two subsequent open-label phase IIIb studies (DREAM and HOPE) enrolled approximately 2,300 former phase III trial participants who were HIV negative and not pregnant; ring use increased when compared with the original phase III studies, with no safety or resistance concerns.^{23,25} Participants were seen every 3 months, compared with monthly visits in the original phase III studies, and adherence remained constant indicating persistent use over the study period. Modelling data suggest an overall 50% reduction in the risk of acquiring HIV across both studies.^{23,25,26} The lack of a placebo arm in these studies is a limitation but these trials indicate a promising trend towards greater adherence and efficacy when users are given an active product that they know is safe and effective.^{23,25} Among women whose returned used rings showed the highest levels of dapivirine release, the risk reduction was as high as 91%, suggesting that improved adherence (more consistent wear) is linked to greater protection.²⁷ The results from these open-label studies demonstrate that while the DVR is less efficacious at preventing HIV infection than oral PrEP, it could be an acceptable and practical option for women in Africa.

Trials in young women

Despite the phase III studies showing a lack of HIV protection in younger women, interim results from the REACH study found that high adherence to the DVR can be achieved among young women and adolescents aged 16–21 years in Africa.²⁸ Participants used the monthly DVR or oral PrEP for 6 months each, followed by a ‘choice period’ where they were offered either product, or neither, for another 6 months. Participants were provided with a menu of adherence options including daily text messages, weekly telephone check-ins, having another participant as a support buddy, support groups and adherence counselling. Early results indicated that both products were well tolerated and acceptable,²⁸ and the DVR was the favoured product in the choice period, with two-thirds of the participants opting for this method.²⁹ Additional research in a small cohort of US women aged 15–17 years showed that the DVR was acceptable and well tolerated.³⁰ Together, these findings suggest that the DVR is a feasible prevention choice for adolescent girls and young women who cannot or choose not to use daily oral PrEP.

Trials in pregnant and breastfeeding women

In the phase III, placebo-controlled ASPIRE study, 169 patients became pregnant during follow-up (82 in the DVR arm and 87 in the placebo arm).³¹ No differences in pregnancy incidence or outcomes (e.g. live birth, pre-term delivery, pregnancy loss, birth defects and infant growth) were noted between the placebo and DVR arms.³¹ These findings support future safety and efficacy studies of DVR use throughout pregnancy, including the prospective inclusion of pregnant and breastfeeding women.³² Two studies, both in Africa, are on-going among pregnant (DELIVER; ClinicalTrials.gov identifier: NCT03965923)³³ and breastfeeding women (B-PROTECTED; ClinicalTrials.gov identifier: NCT04140266),³⁴ and are evaluating maternal and infant safety with DVRs and daily oral PrEP.³⁵

The phase IIIb trial DELIVER began in February 2020 and, in May 2021, completed the first cohort of 150 women who were HIV negative and 36–37 weeks pregnant when they enrolled.³³ In June 2021, the interim review panel for the DELIVER phase IIIb study found no safety concerns and recommended that the study proceed to enrol the next cohort of 150 pregnant women (30–35 weeks’ gestation).³² The third and final cohort will enrol 250 women at 12–29 weeks’ gestation. The B-PROTECTED trial reached full enrolment of 197 infant–mother pairs in July 2021.³⁴ This study follows previous research (the MTN-029 trial) that detected very low concentrations of dapivirine in the breast milk of participants using the DVR.³⁶

Regulatory pathway

In July 2020, the European Medicines Agency provided a positive scientific opinion on the DVR as a HIV prevention option for women aged 18 years and older who are unable to use oral PrEP.³⁷ The World Health Organization (WHO) recommended the DVR as a new choice for HIV prevention for women at substantial risk of HIV infection, and the DVR was included in the WHO pre-qualification list in January 2021.³⁸ This means that the DVR meets global standards for quality, safety and efficacy, and helps guide national and global procurement decisions. The DVR application was submitted to SAHPRA by IPM, and was approved on 8 March 2022 for use in HIV-negative non-pregnant women aged 18 years and older; it is registered under the name 'DapiRing vaginal delivery system'.³⁹ It is registered as a schedule 4 drug, meaning that any appropriately trained healthcare provider is authorized to assess, diagnose, prescribe and dispense.

In December 2021, IPM voluntarily withdrew the dapivirine new-drug application from the US Food and Drug Administration (FDA) after receiving feedback that, given the HIV epidemiology in the USA, where the epidemic is primarily among men and there are other more effective options, it was unlikely that the product would be licensed in the USA.⁴⁰

In June 2022, the Department of Health in South Africa released an evidence review as part of the primary healthcare medication review process. The committee recommended that the DVR not be used as an additional prevention option (conditional recommendation). Reasons include a lack of evidence around key indicators including efficacy in adolescents and during pregnancy, no data comparing oral PrEP with the DVR, and cost. The decision could be updated with emerging evidence around key indicators.⁴¹

Extended-duration dapivirine rings and multi-purpose prevention technologies

Recognizing that an even longer-acting DVR could further expand options, researchers developed a 3-month DVR with the hope that this may offer more convenience and reduce cost. A phase I study of the extended-duration DVR showed that it was well tolerated and achieved higher dapivirine concentrations compared with the monthly DVR.⁴²

HIV and pregnancy complications are among the greatest threats to women's health and well-being. Studies have shown that women may be 2–4 times more likely to acquire HIV during pregnancy and the post-partum period.⁴³ As well, HIV-positive women may face an increased risk of maternal death than HIV-negative women.⁴⁴ Multi-purpose products (MPTs) that can address both contraception and HIV prevention simultaneously could help women to stay healthy. Women's perceived risk of pregnancy may be higher than their perceived risk of HIV, and combined technologies may be attractive to many women and providers. Two safety studies of IPM's 3-month dapivirine–levonorgestrel contraceptive ring found the ring to have a promising safety profile with encouraging drug levels for both HIV prevention and contraception.⁴⁵ Phase I studies are due to start in 2022.

The importance of choice

No single prevention method or approach can stop the HIV epidemic on its own. Powerful lessons from the contraception field have demonstrated that expanding the product options and increasing choice will likely increase coverage over the different HIV prevention methods.⁴⁶ Preference depends on context and may vary according to timing, life stage and new relationships, and requires choice.⁴⁷ A systematic review of

adherence to oral PrEP highlighted that side effects, incompatible dosing regimens and stigma were some of the main reasons for non-adherence.⁴⁸ Discreet, long- and locally acting products like the DVR may provide a viable solution to these challenges. Providing choice could better cover the diverse population of women and types of HIV exposure. With the DVR under review by several African regulators, policymakers, donors and implementers must now consider the role of the DVR in the prevention menu and how the oral PrEP implementation experience could guide decision-making.

Pre-exposure prophylaxis in South Africa

South Africa was the first country in Africa to license oral PrEP in December 2015.⁴⁹ The National Department of Health phased its implementation, starting with roll-out at facilities providing services to sex workers in 2016, then expanding in 2017, first to men who have sex with men and then to students at select colleges and universities, followed most recently by roll-out at government clinics.⁵⁰ An application has been made to SAHPRA for a third PrEP option in the form of long-acting cabotegravir (CAB-LA). Results from two phase III trials found that injectable cabotegravir, given every two months, was an effective PrEP option in preventing HIV in cisgender women, men who have sex with men, and transgender women.^{51,52}

To realize the benefits of PrEP, users need to be able to access and remain on PrEP during periods of risk.⁵³ Women also need near-perfect adherence to PrEP to achieve the kind of tissue concentrations needed for protection.⁵⁴

Data from the Department of Health in South Africa demonstrate that by the end of 2021, 450,606 people had accessed PrEP since its introduction, with 286,068 people accessing PrEP in 2021.⁵⁵ Overall, 1.9% of young women aged 20–24 years and 1.5% of young women aged 15–19 years have accessed PrEP, with significant differences between provinces. The doubling of PrEP uptake between 2020 and 2021, when PrEP became more widely available, demonstrates that there is a demand for HIV prevention, with young women aged 15–24 years being the largest PrEP user group.⁵⁶

While oral PrEP has been an important addition to the prevention package, there have been challenges to scaling up provision.⁵⁶ These have included issues relating to uptake, continuation rates, effective use, challenges with taking a daily pill, side effects and stigma, in addition to unpredictable sexual patterns among young users, and the lack of understanding of people's sexual risk periods, with the associated complexities relating to cycling on and off oral PrEP. These all point to the need for additional PrEP options, including those that are more discreet, are less frequently dosed and, therefore, not reliant on daily adherence, and that have no systemic side effects.⁵⁷

Lessons learnt from pre-exposure prophylaxis that will guide implementation decisions

A review of oral PrEP implementation in sub-Saharan Africa provides five key learnings that can be used to guide thinking around DVR implementation.² Scaling back on risk assessments and eligibility criteria for oral PrEP and, rather, providing it to all who requested it removed unnecessary barriers to use. In addition, reducing complexity around prescription was important for scale-up. The safety profile of the DVR allows it to be made available for all who request it and, if HIV self-testing is found to be feasible, this could further enhance access in diverse settings.²

Diversified service-delivery channels improved PrEP uptake, especially in young women, and consideration should be given to providing the DVR outside of health clinics, using mobile services, community-based venues and pharmacies.² Multi-month dispensing and virtual adherence support could also improve access and uptake.

Training health workers to provide youth-friendly services improved PrEP uptake. Continued education and training will be important to support the uptake and effective use of this form of PrEP that will be unfamiliar to most potential users and health workers.² Health workers will also need training to support users to make informed choices between multiple options.

Innovative communication campaigns aimed at improving partner and community acceptance of PrEP were necessary to create demand. Sustained demand creation and engagement of partners and peers will be critical for this new and unknown vaginal product. Positive messaging developed for PrEP around well-being, empowerment and pleasure will be equally applicable to the DVR.²

Understanding the effective use of PrEP required new language and different thinking compared with traditional treatment frameworks. Support of effective DVR use will require further understanding of periods of risk and patterns of use. Tools that support users to make informed decisions will likely help.²

Cost and cost-effectiveness

The cost to manufacture a single DVR is US\$7 (ZAR115) with the understanding that, in low- and middle-income countries, the DVR will be provided for free to women at primary care clinics.⁵⁸ Evidence from several studies suggests that the DVR is expected to cost less than oral PrEP because it requires fewer health-system resources.² When the cost-effectiveness studies were done for oral PrEP, the price of baseline investigations including HIV testing, creatinine clearance and hepatitis B antigen testing were considered in the calculations. The only test required for delivering the DVR is an HIV test.² One study from South Africa suggested that the DVR would be a cost-saving intervention for the KwaZulu-Natal province if it were given to female sex workers, and could have a substantial impact if prioritized for women at substantial risk of HIV or women aged 22–29 years.²⁶ One study used the Goals model to assess the impact of the DVR across countries with high rates of HIV infection, and found that, although the DVR has the potential to significantly reduce infections, the impact is highly variable and depends on antiretroviral therapy coverage and oral PrEP scale-up.⁵⁸

Acceptability and feasibility

A review including 11 articles and abstracts looking at DVRs for HIV prevention found that the use of vaginal rings was highly acceptable (71–98% in randomized controlled trials and 62–100% in observational studies), and most participants reported that the DVRs were easy to use.⁵⁹ The review also noted that DVR acceptability increased as the DVR became more common in communities and women became more

comfortable with its use. Partner perception and influence were also noted as strong factors influencing DVR use, and perceived community support and acceptance of DVR use were important.⁵⁹

A systematic review and meta-analysis assessing the global acceptability of any type of vaginal ring noted that generally, rings were highly acceptable and that most women who had used a ring liked it; whereas women who had not used a ring before said that they did not think they would like to use this kind of device, suggesting that supporting women to try the ring may be a critical part of increased uptake.⁶⁰

Multiple studies of the DVR have been conducted across both rural and urban areas in South Africa, proving its feasibility across settings where the ring is intended to be implemented.^{12,23,25} The DVR is easy to transport and store, and does not require refrigeration.⁶¹

What is the potential impact of the dapivirine vaginal ring?

Modelling studies show that prevention methods like the DVR could have a meaningful public health impact through the provision of choice, and could avert infections that would not be prevented by another method. Expanded options and long-acting methods are needed to increase the uptake of HIV prevention methods among women, especially in generalized epidemics.⁵⁸ Remaining HIV negative and in control of your own health and future has intangible value to both individuals and society, and cost should not be the only consideration when implementing prevention programmes.⁵⁷

Research gaps

The use of the DVR in key population groups like sex workers has not been researched.⁵⁷ Modelling studies show that introducing the DVR to sex workers could substantially impact HIV prevention.²⁶ Research is urgently needed to understand ring acceptability in this group.

As new prevention options are introduced, women may choose to switch between the different options or even use more than one at a time. These possible patterns of use are currently not known or understood, and require careful support and assessment.⁶² As South Africa is poised to introduce both the DVR and CAB-LA, implementation research will be needed to strategically and quickly maximize the impact of both interventions.

Conclusion

Licensing of the DVR in South Africa is an achievement that brings the first long-acting and woman-controlled product another step closer to reaching the people who need it. Ending the HIV epidemic will require optimal implementation and scale-up of existing treatment and prevention modalities. In South Africa, the country that has been the hardest hit by the HIV pandemic, and where women bear the brunt of the disease, it may be all about options because a product that best suits a woman's preferences and needs is much more likely to be used consistently and correctly with a greater prevention impact. □

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